Drs. Andervont
Huebner
Meier

CARCINOGENESIS

THE COUNCIL FOR TOBACCO RESEARCH—U.S.A., INC.

110 EAST 59TH STREET
NEW YORK, N. Y. 10022
(212) 421-8887

JUL 16 1973

Application for Research Grant
(Use extra pages as needed)

Date: 7/9/73

1. Principal Investigator (give title and degrees):

Joseph C. Arcos
Professor of Medicine (Biochemistry)
L. Chem., Ch. E., D. Sc.

Mailing address:

Seamen's Memorial
Research Laboratory
USPHS Hospital
210 State Street
New Orleans, La. 70118

2. Institution & address:

Tulane University School of Medicine
1430 Tulane Ave.
New Orleans, La. 70112

3. Department(s) where research will be done or collaboration provided:

Department of Medicine

4. Short title of study: Synergistic effects of polycyclic hydrocarbons and nitrosamines in pulmonary carcinogenesis. Potential repressors of metabolic activation of nitrosamines.

5. Proposed starting date: 1/1/74

6. Estimated time to complete: 4 years *

7. Brief description of specific research aims:

First, to explore experimentally the very definite possibility (see 8. Background and brief statement of working hypothesis) that a significant proportion of the lung tumor incidence of cigarette smokers is due to synergism between hydrocarbons and nitrosamines present in the smoke rather than to the hydrocarbons alone, and that the oral nitrosamine intake of smokers (as dietary nitrosamine contaminants, or pro-nitrosamine additives such as nitrite together with ubiquitously present secondary amines in meat products) could play an important role in their high lung cancer incidence. Second, to investigate

* It is understood that The Council makes renewal awards usually up to 3 years. However, special consideration should be given to the fact that this proposal involves a substantial number of carcinogenesis bioassay systems in which each animal group will have to be maintained for 18 months, followed then by the autopsy of large numbers of animals, histopathology of the tissues, and analysis and organization of the data. Consequently, to keep the experiment manageable, it will be necessary to stagger certain experimental segments within the present study.

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7. continued...

whether certain nontoxic inhibitors of nitrosamine metabolism — a process known to be required for carcinogenesis by these agents — also inhibit nitrosamine carcinogenesis and, hence, would decrease lung tumor incidence by disrupting the hydrocarbon-nitrosamine synergism.

Any bioassay of potential carcinogens or combination(s) thereof must be carried out for a minimum of 1 year, to be meaningful at all, unless a statistically significant percentage of tumor incidence is reached earlier (1); the same holds, evidently, when intending to establish synergistic and co- and anti-carcinogenic effects relative to control group(s) in specific experiments. For this reason it will require a number of years to explore all aspects of the hydrocarbon-nitrosamine carcinogenic synergism in the lung as well as the possible means of disrupting this synergism.

The present proposal represents the first segment of this approach. In this study we will investigate the synergism toward lung tissue of the highly carcinogenic hydrocarbons, 3,4-benzopyrene and 3,4-benzofluoranthene, with the carcinogenic nitrosamines, dimethylnitrosamine, methylethylnitrosamine, and N-nitrosopiperidine — all present in cigarette smoke. In the present study all hydrocarbon-nitrosamine combinations will be given orally, the route of administration by which the first instance of synergism of this type, with a combination of 3-methylcholanthrene and dimethylnitrosamine, was demonstrated in our laboratory (2). Also within the framework of the present study we intend to determine the inhibitory effect of β-naphthoflavone and pregnenolone-16α-carbonitrile on the carcinogenic activity of dimethylnitrosamine; these two agents are powerful inhibitors of dimethylnitrosamine metabolism, and are virtually nontoxic.

8. Background and brief statement of working hypothesis:

A.) Hydrocarbon-nitrosamine synergism. — A previous study (2) in our laboratory has shown that administration of 3-methylcholanthrene inhibits liver tumor induction in rats by simultaneously administered dimethylnitrosamine. In a series of investigations (3-7) we have established that this is due to inhibition in the liver of the biosynthesis of the enzyme, dimethylnitrosamine-demethylase, the key enzyme transforming this nitrosamine to its actual carcinogenic metabolite.

An unexpected and important finding of the carcinogenesis study (2) was that while the hepatocarcinogenicity of dimethylnitrosamine is inhibited by the simultaneous oral administration of 3-methylcholanthrene, the two agents have a powerful synergistic effect in lung tumor induction. Indeed, whereas at the levels used in the study neither the nitrosamine nor the hydrocarbon alone was carcinogenic in the lung, combined administration of the two agents brought about a 15% pulmonary tumor incidence. The practical significance of this lies in the facts (a) that 3-methylcholanthrene is known to be very similar or identical in action to the two potent hydrocarbon carcinogens, 3,4-benzopyrene and 3,4-benzofluoranthene, present in cigarette smoke (8), and (b) that dimethylnitrosamine, methylethylnitrosamine, and N-nitrosopiperidine are also present in the smoke (9) at a

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total level of similar order of magnitude as the hydrocarbons (10). Dimethylnitrosamine and N-nitrosopiperidine are well-known to be potent carcinogens; although methylethylnitrosamine has not been assayed as yet, from what is known about the structure-activity relationships of the dialkylnitrosamines there is no doubt that it will prove to be carcinogenic since both dimethyl- and diethylnitrosamine are potent agents.

The above considerations point to the high probability that a significant proportion of the lung tumor incidence of smokers is due to synergism between carcinogenic hydrocarbons and nitrosamines present in the smoke, rather than to the hydrocarbons alone. Thus, the present approach will open hitherto neglected or unsuspected approaches toward a "safer" cigarette. The working hypothesis has also wider ramifications — to be explored in subsequent phases of this approach — in that a proportion of the lung tumor incidence of smokers could be due, in addition to the hydrocarbons (and nitrosamines) present in the smoke, to particular pattern(s) of diet rich in nitrosamine contaminants or pro-nitrosamine components (i. e., nitrite plus secondary amines).

In the present study administration of both hydrocarbons and nitrosamines will be by oral route to follow the pattern of the previous report (2) which showed that pulmonary synergism does exist between 3-methylcholanthrene and dimethylnitrosamine. In subsequent phases — for approximating more closely the actual human situation — we intend to investigate the synergistic effect of orally administered nitrosamines [and pro-nitrosamine components: nitrite plus secondary amine(s)] with intratracheally instilled hydrocarbons, and then with smoke of known 3, 4-benzopyrene level. Since orally received nitrosamines may also be synergistic with hydrocarbons entering the lung via the trachea, these represent an experimental model exploration of the role of dietary nitrosamines on the lung tumor incidence of smokers. Subsequent phases of this approach will also include exploration of the possible carcinogenesis promotor effect of noncarcinogenic polycyclic hydrocarbons, present in cigarette smoke and found recently to be cocarcinogenic (11), upon pulmonary carcinogenesis by nitrosamines.

A.) Hydrocarbon-nitrosamine synergism — A previous study (2 in our [illegible] B.) Anti-carcinogenic effects of β-naphthoflavone and pregnenolone-16α--carbonitrile. — We have demonstrated that not only polycyclic hydrocarbons but also phenobarbital (3, 4), as well as aminoacetonitrile, β- naphthoflavone and pregnenolone-16α-carbonitrile (7) inhibit the critical metabolic route of dimethylnitrosamine leading to its actual carcinogenic metabolite. Kunz et al. (12) reported that administration of phenobarbital inhibits the carcinogenicity of diethylnitrosamine, and Hadjiolov (13) found that administration of aminoacetonitrile inhibits the carcinogenicity of dimethylnitrosamine.

It is well established that β-naphthoflavone inhibits the carcinogenic action of certain hydrocarbons (e. g., 14, 15). It is unknown as yet whether β-naphthoflavone and pregnenolone-16α-carbonitrile inhibit carcinogenesis by nitrosamines, but from the established evidence that they powerfully inhibit the obligatory metabolic route of dimethylnitrosamine, it is expected that they will be found to be potent inhibitors of nitrosamine carcinogenesis. Since neither of two compounds is carcinogenic, they show definite promise as effective agents to disrupt the hydrocarbon-nitrosamine pulmonary synergism.

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9. Details of experimental design and procedures:

For investigating the synergistic carcinogenic effects toward the lung of 3, 4-benzopyrene and 3, 4-benzofluoranthene, on one hand, and dimethylnitrosamine, methylethylnitrosamine, and N-nitrosopiperidine, on the other, the general conduct of the bioassays will be patterned on our previous study with 3-methylcholanthrene and dimethylnitrosamine (2). The "Synoptic Tabulation of Bioassay Groups" shows the overall experimental design of the synergism experiments and of the experiments on the anti-carcinogenic action of β-naphthoflavone and pregnenolone-16α-carbonitrile.

Hydrocarbon-nitrosamine synergism. — The present experimental design includes certain modifications of the procedure followed in the previous study (2). A minimum of 60 rats serving as negative controls will be maintained parallel with the experimental groups. These rats will receive by stomach tube aqueous methylcellulose (Methocel) solution (the medium used to administer the hydrocarbons in the experimental groups) in the same amount, following the same schedule, and for the same length of time, as the respective experimental groups receiving the hydrocarbons in suspension in that same medium. These negative controls will be divided into 2 or 3 groups and started so as to coincide with the beginning of staggered experimental segments (see Footnote on p. 1). As in the previous study (2) male Sprague-Dawley rats, weighing 180-220 gm initially will be used. We do not plan at this stage to explore the sex-dependence of the synergistic effects studied; however, this will be incorporated in our studies of this phenomenon in subsequent stages of this approach.

3, 4-Benzopyrene and 3, 4-benzofluoranthene will be administered at levels equimolar to 300 μg 3-methylcholanthrene daily 5 times a week (2); this amounts to a daily dose of 282 μg for both hydrocarbons in view of their identical molecular weights. Dimethylnitrosamine will be administered by stomach tube at the same daily dose level (400 μg) as previously (2); however, the length of administration will be extended from 24 to 26 weeks in the expectation of better approximating the TD_{50} dose. The daily doses of methylethylnitrosamine and N-nitrosopiperidine will be equimolar to 400 μg of dimethylnitrosamine; these daily doses are 480 μg and 650 μg, respectively. Methylethylnitrosamine will be administered for 22 weeks for approaching an approximate 50% tumor incidence; this is the best approximation possible for the TD_{50} dose of this nitrosamine, based on an interpolation from some dimethyl- and diethylnitrosamine dose-response data (16, 17). N-Nitrosopiperidine will be administered for 28 weeks; this is based on the dose-response data of Druckrey et al. (18).

The length of administration of both hydrocarbons will run a middle course between the shortest and longest duration of administration of the three nitrosamines studied, i.e., 25 weeks. However, in the groups receiving both a hydrocarbon and a nitrosamine, administration of the hydrocarbon will always be initiated 1 week before the beginning of nitrosamine administration.

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Synoptic Tabulation of Bioassay Groups.

	Compound:	No. of animals:	Daily dose (µg):	Medium of administration:	Length of administration (weeks):
	Negative controls	60	—	Methocel 1%	28
Pulmonary Synergism	3,4-Benzopyrene (BP)	40	282	Methocel 1%	25
	3,4-Benzofluoranthene (BzF)	40	282	— " —	25
	Dimethylnitrosamine (DMN)	40	400	Water	26
	Methylethylnitrosamine (MEN)	40	480	— " —	22
	N-Nitrosopiperidine (NPiP)	40	650	— " —	28
	BP & DMN	40	282 & 400	Methocel & Water	25 & 26
	BP & MEN	40	282 & 480	— " —	25 & 22
	BP & NPiP	40	282 & 650	— " —	25 & 28
	BzF & DMN	40	282 & 400	Methocel & Water	25 & 26
	BzF & MEN	40	282 & 480	— " —	25 & 22
	BzF & NPiP	40	282 & 650	— " —	25 & 28
Inhibition of Carcinogenesis	DMN	40	400	Water	28
	β - Naphthoflavone (NF)	40	20 mg/kg	in diet	29
	Pregnenolone-16α--carbonitrile (PCN)	40	20 mg/kg	in diet	29
	DMN & NF	40	400 µg & 20 mg/kg	Water & diet	28 & 29
	DMN & PCN	40	400 µg & 20 mg/kg	Water & diet	28 & 29

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After the schedules of carcinogen administration will be terminated, the animal groups will be maintained for an additional 11-12 months (2). Following the routine procedure in our laboratory, during this observational period the animals will be checked twice daily and the state of their health carefully followed. During this observational period any animal showing clear evidence of the presence of a tumor (i. e., large subcutaneous or abdominally localized), or morbidity, will be sacrificed, submitted to complete autopsy, and the tissue samples fixed in neutral formaline for histopathology. All survivors will be sacrificed at the end of the observational period and treated as above. Histopathology will be carried out by Dr. Joseph Simon, Professor of Pathology, College of Veterinary Medicine, University of Illinois, Urbana, and by Dr. Cornelia Hoch-Ligeti, Chief, Pathology Service and Research Laboratory, Veterans Administration Center, Martinsburg, W. Va., with whom we have had excellent collaboration for the last 15 years.

Anti-carcinogenic effects of β-naphthoflavone and pregnenolone-16α-carbonitrile. — As it has already been described in "Background and brief statement of working hypothesis" these two compounds are powerful inhibitors of the demethylation of dimethylnitrosamine, the metabolic route which is the controlling step of tumor induction by this agent. Thus, combined administration of either of these two compounds with dimethylnitrosamine should decrease the carcinogenicity of the nitrosamine.

Since both β-naphthoflavone and pregnenolone-16α-carbonitrile are costly compounds, it was necessary to determine first the lowest dietary levels at which saturation of dimethylnitrosamine-demethylase inhibition is reached. In a preliminary study of the dose-dependence of inhibition of dimethylnitrosamine-demethylase biosynthesis by in vivo administered pregnenolone-16α-carbonitrile we found that 22-25 mg/day/kg body weight is slightly beyond the saturation dose for inhibition. This is also the appropriate dose for β-naphthoflavone to reach saturation level, as indicated by a comparison of our preliminary data with the results of Cantrell and Bresnick (19). Thus, in the respective groups the animals will receive β-naphthoflavone and pregnenolone-16α-carbonitrile at a daily dose of 25 mg/day/kg body weight, incorporated in the diet.

To increase the likelihood of a better statistical significance (if our working hypothesis is successful) between the DMN control group and the experimental groups receiving DMN + NF and DMN + PCN, the total dose level of dimethylnitrosamine will be set to the 75% rather than the 50% tumor incidence level. We approximate that this will require administering nitrosamine for 28 weeks at the 400 μg daily dose. Administration of the two inhibitors will start 1 week prior to the beginning of dimethylnitrosamine administration. As in the synergism experiments, following termination of the administration schedule the animals will be maintained for an additional observational period of 11-12 months. Maintenance of the animals, autopsies, and histopathology will be as above.

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References:

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(2) Hoch-Ligeti, C., Argus, M. F., and Arcos, J. C. : "Combined Carcinogenic Effects of Dimethylnitrosamine and 3-Methylcholanthrene in the Rat". J. Natl. Cancer Inst. 40, 535 (1968).

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(5) Venkatesan, N., Arcos, J. C., and Argus, M. F. : " Amino Acid Induction and Carbohydrate Repression of Dimethylnitrosamine Demethylase in Rat Liver". Cancer Res. 30, 2563 (1970).

(6) Argus, M. F., Valle, R. T., Venkatesan, N., Buu-Hoi, N. P., and Arcos, J. C. : "Molecular-size-dependent effects of polynuclear hydrocarbons on mixed-function oxidases: possible action on cascade-coupled operons". Proc. 1st Europ. Biophys. Congr. EI/38, 187 (1971).

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(9) Wynder, E. L. : "Environmental Carcinogenesis and Cocarcinogenesis". Presented in Pharmacol. Symp. on "Mechanisms of Chemical Oncogenesis". 57th Federation Meet., Atlantic City, 1973, April 17.

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(11) Goldschmidt, B. M., Katz, C., and VanDuuren, B. L. : "The Cocarcinogenic Activity of Noncarcinogenic Aromatic Hydrocarbons". Proc. Am. Assoc. Cancer Res. 14, 84 (1973).

(12) Kunz, W., Schaude, G., and Thomas, C. : "Die Beeinflussung der Nitrosamincarcinogenese durch Phenobarbital und Halogenkohlenwasserstoffe". Z. Krebsforsch. 72, 291 (1969).

(13) Hadjiolov, D. : "The Inhibition of Dimethylnitrosamine Carcinogenesis in Rat Liver by Aminoacetonitrile". Z. Krebsforsch. 76, 91 (1971).

(14) Wattenberg, L. W., and Leong, J. L. : "Inhibition of the Carcinogenic Action 7, 12-Dimethylbenz[a]anthracene by β-Naphthoflavone". Proc. Soc. Exp. Biol. Med. 128, 940 (1968).

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(16) Argus, M. F., and Hoch-Ligeti, C. : "Comparative Study of the Carcinogenic Activity of Nitrosamines". J. Natl. Cancer Inst. 27, 695 (1961).

(17) Arcos, J. C., Argus, M. F., and Mathison, J. B. : "Hepatic Carcinogenesis Threshold and Biphasic Mitochondrial Swelling Response in the Guinea-Pig During Diethylnitrosamine Administration". Experientia 25, 296 (1969).

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Vol. I. Academic Press. 1961. p. 342

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10. Space and facilities available (when elsewhere than item 2 indicates, state location):

The Seamen's Memorial Research Laboratory at the U. S. Public Health Service Hospital has a total laboratory area of 4800 square feet, plus air-conditioned animal quarters of a total of 3000 square feet. The applicant has at his disposal approximately 1400 square feet of laboratory space, including a well-equipped cold room, approximately 2400 square feet of animal quarter space, and adequate office space. This is made available to the applicant through the Tulane Department of Medicine.

The major equipment in the applicant's laboratory space consists of the following: a Beckman DB spectrophotometer with recorder, a Shimadzu spectrophotometer with flow dichroism attachment, 4 Coleman spectrocolorimeters, a Photovolt fluorimeter, a Brice-Phoenix light-scattering photometer complete with ratio recorder, an Abbe refractometer, a Rudolph manual spectropolarimeter, 2 fourteen-manometer Warburg apparatuses, a "Yellow Springs" recording oxygen monitor, a high wattage ultrasonic generator, two analytical balances, several pH meters, a semi-automatic tensiometer, a "Spinco L" preparatory ultracentrifuge (including swinging bucket rotor and other accessories for polysome profiling), 3 "Servall" high-speed table centrifuges, 2 heavy-duty International model V centrifuges, a starch-block electrophoresis apparatus with circulating cooling system, a lyophilizing apparatus, 2 heating and cooling precision waterbaths, a Dubnoff waterbath incubator shaker; refrigerators, a deep freeze unit, an incubator. The use of a Microtech gas chromatograph and of an osmometer are available in the laboratory.

11. Additional facilities required:

Two project sites were given in the Summary Outline of this proposed project submitted to Dr. Hockett in our letter of May 25. The second site listed is very spacious and most modern animal quarters which our Department puts at our disposition in its newly acquired building (built 5 years ago by the Ethyl Corporation) which houses the Laboratory of Environmental Medicine. Although our animal facilities at the Seamen's Memorial Research Laboratory are adequate, in view of the potentially critical significance of this project for public health and for the cigarette industry, it would be preferable if the project could be carried out in these most up-to-date quarters. However, for us to be able to effectively occupy, in the newly acquired building, laboratory space commensurate with this project, we would need funds for installation costs and for adapting the space to our specific needs of bioassay studies. It is estimated that the costs to prepare space for this project in the Laboratory of Environmental Medicine would amount to $11,200.

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12. Biographical sketches of investigator(s) and other professional personnel (append):

Curricula of three investigators appended.

13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available).

List of 10 publications see next page (reprints appended).

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13. Publications: (reprints enclosed).

(1) Argus, M. F., Sohal, R. S., Bryant, G. M., Hoch-Ligeti, C. and Arcos, J. C. : "Dose-Response and Ultrastructural Alterations in Dioxane Carcinogenesis. Influence of Methylcholanthrene on Acute Toxicity". Europ. J. Cancer 9, 237 (1973).

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14. First year budget:

A. Salaries (give names or state "to be recruited") Professional (give % time of investigator(s) even if no salary requested)	% time	Amount
Joseph C. Arcos, D. Sc.	R	R
Mary F. Argus, Ph. D.		
Joseph Simon, D.V.M., Ph. D.		
Technical		
Georgia M. Bryant, B.A., Technician	25%	$ 2,300
Laboratory Technician (to be recruited)	100%	$ 6,000
Laboratory Technician (to be recruited)	100%	$ 6,000
Animal caretaker (to be recruited)	100%	$ 4,450
Secretary (to be recruited)	40%	$ 2,700
	Sub-Total for A	25,450
B. Consumable supplies (by major categories)		
Animals		$ 1,200
Animal feed		1,600
Carcinogens & other Chemical Agents		2,400
Glassware		300
Animal Bedding & cleaning supplies for animal quarters		1,100
	Sub-Total for B	6,600
C. Other expenses (itemize)		
Installation & costs of adapting existing space for bioassay purposes (see 11.Additional facilities required)		$11,200
	Sub-Total for C	11,200
	Running Total of A + B + C	43,250
D. Permanent equipment (itemize)		
	Sub-Total for D	
E. Indirect costs (16% of A+B+C)	E	6,488
	Total request	49,738

15. Estimated future requirements: (see p. 12)

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2	27,000	4,500	4,000	3,000	5,325	43,825
Year 3	28,600	3,300	9,000		6,135	47,035
Year 4	25,600	1,400	9,000		5,400	41,400

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Explanation of estimated requirements for future budget years:

1.) The salary category decreases in the 4th year, despite the annual increases, because we estimate that 1 technician will become unnecessary in the last 8 months of this project.

2.) The consumable supplies will be very low in the 4th year because the animal groups to be maintained are tapering off at that time.

3.) The category "Other Expenses" are histology costs. These are the lowest in the second year because the first experimental segment will begin to be processed for histopathology at the end of the second year. The major part of the histology cost requirements are distributed over the 3rd and 4th year.

4.) The category "Permanent Equipment" in the 2nd year is the cost to purchase replacement cages and racks. These will have to be purchased at the end of the 2nd year.

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16. Other sources of financial support:
List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Faculty Research Award (exclusively salary grant)	American Cancer Society	127,887	1/1/72 - 12/31/76
Pharmacology of Repressible Mixed-Function Oxidases	NCI CA-13206	111,626	1/1/72 - 12/31/74

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Pharmacology & Biochemistry of the Oncogen, Dioxane	NCI CA-15111	384,390	9/1/73 - 8/31/78
Control of Catabolism of Mitochondria in Oncogenesis	NCI	182,327	1/1/74 - 12/31/77

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name Joseph C. Arcos, D. Sc.

Signature Joseph Arcos Date 7/9/73

Telephone (504) 899-3441 331
Area Code Number Extension

Checks payable to

Tulane University

Mailing address for checks

Jesse B. Morgan, Comptroller

Tulane University, Station 20

New Orleans, La. 70118

Responsible officer of institution

Typed Name William G. Thurman, M. D.

Title Dean, Tulane Univ. School of Medicine

Signature William G. Thurman 7/9/73

Telephone (504) 588-5462
Area Code Number Extension

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CURRICULUM VITAE OF JOSEPH CHARLES ARCOS

PERSONAL DATA:

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Professional address:

Seamen's Memorial Research Laboratory
U. S. Public Health Service Hospital
210 State Street
New Orleans, Louisiana 70118

EDUCATIONAL BACKGROUND:

Undergraduate studies:

Secondary school: Gymnasium Baccalaureate degree (humanities - science). Nagykanizsa (Hungary), 1939.

1944-47. University "Bolyai" of Cluj (Roumania), Faculty of Sciences. "Licentiate in Chemistry" degree (minor: physics), "cum laude," 1947. Literature Thesis on "Chemistry and Physiological Effects of Vitamin D."

Graduate studies:

1947-50. Conservatoire National des Arts et Métiers, Paris, France. "Chemical Engineer" degree (major: dye chemistry; minor: industrial processes), "with felicitations," 1950. Thesis: "Synthèses de quelques nouveaux dérivés de la cystéine." (Synthesis of aminosulfonic, aminosulfinic and oxysulfonic acids related to cysteine and the separation of optical isomers). Subsequently, study of the competitive antagonism of these isomers with the isosteric aspartic acid in Lactobacillus helveticus and L. arabinosus.

1949-51. University of Paris, France. Faculty of Sciences. Preparation of a Doctoral Dissertation at the Collège de France. "Doctor in Science" degree in organic chemistry, "magna cum laude," 1951. Dissertation: "Recherches sur les diquinols mésodiphénylanthracéniques aminés. Étude sur la 'migration méso'." (Synthesis and photooxidation of hydroxy and amino derivatives of 9,10-diphenylanthracene. Elucidation of a new intramolecular rearrangement - leading to substituted anthrones). Literature Thesis (2nd Thesis): "La chimiothérapie de la lèpre."

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Post-graduate training:

1948: "Techniques in Physiology and Pharmacodynamics" (lectures and laboratory). Faculty of Medicine, University of Paris.

1951: Training periods in dye chemistry (syntheses and physicochemical studies), Francolor Co., Saint-Denis, France, and Imperial Chemical Industries, Manchester, England.

1952: "Oncology" (lectures and laboratory). Institut du Cancer "Gustave Roussy," University of Paris, Villejuif, France.

1969: American Chemical Society short course in "Molecular Orbital Theory." Houston, Texas.

POSITIONS:

1968- Professor of Medicine (Biochemistry). 1960-1968: Associate Professor of Medicine (Biochemistry), Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana 70112.

Principal research orientations: Alterations of mitochondrial electron transport parameters and membrane dynamics in the rat liver during hepatocarcinogenesis induced by amino azo dyes and nitrosamines, and in the rat heart during thiamine deficiency, following exercise, and following aortic constriction. Enzymology of extramitochondrial NADH oxidation. Phase-transitions in the mitochondrial membrane and change of stereochemistry of electron transport-related sulfhydryl groups during azo dye carcinogenesis; the use of dicarbonyl probes. Mechanism of apparent mitochondrial multiplication during feeding of noncarcinogenic azo dyes. Change of the electrophoretic pattern and sulfhydryl level in the soluble supernatant proteins of the rat liver in various situations of rapid growth. Structure-activity relationships of carcinogenic compounds in relation to their molecular geometry. Mechanism of dioxane carcinogenesis. Mechanism of protein denaturation by nitrosamines and related carcinogens; study of their hydrogen bonding ability. Effect of polynuclear hydrocarbons on microsomal azo dye and dimethylnitrosamine (DMN) metabolism in relation to their molecular geometry. Functional and kinetic characteristics of DMN-demethylase, the key enzyme of DMN carcinogenesis. Pre-repair geometry of nuclear DNA during DMN carcinogenesis. Genetic control of DMN-demethylase synthesis.

1957-1960: Assistant Research Professor, Cancer Research Laboratory, Department of Pharmaceutical Chemistry, University of Florida, In charge of the Section of Biophysical Chemistry.

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Research orientations: Alterations of the swelling of mitochondria in the rat liver during feeding amino azo dyes and other hepatic carcinogens, and in azo dye hepatomas; relationship with the onset of tumorigenesis. Non-linearity of the carcinogenic response. Effect of SH-reactants on mitochondrial swelling. Antagonism and synergism between carcinogenic azo dyes.

1953-1957: Project-Associate, McArdle Memorial Laboratory for Cancer Research, University of Wisconsin

Research orientations: Synthesis of derivatives of diphenylamine and of benzo(c)cinnoline, related to the mechanism of carcinogenesis by p-dimethylaminoazobenzene. Biological testing. The relation of molecular dimensions and of structural geometry to carcinogenic activity. Electrophoretic pattern and quantitative separation of fractions of the supernatant protein and of solubilized microsomal proteins of the rat liver; analysis of the amino acid composition, vitamin, nucleic acid and azo dye content of the fractions. Alterations of the swelling of rat liver microsomes during feeding of carcinogenic and noncarcinogenic azo dyes, and of azo dye hepatoma microsomes. Covalent binding of azo dyes to microsomes. Influence of various parameters on microsomal swelling.

1952-1953: Technical Assistant-Director. Jouan Company, Paris, France, manufacturers of laboratory apparatus. Planning and development of prototypes of a new closed circuit flame photometer, a semi-automatic polarograph, a differential galvanometer for the recording of hypo- and hyperthermy, a glossometer for the manufacturing of paper. Reorganization of the electronics division.

1952: Research Engineer. Technical Center of Graphic Industries, Paris, France. Physico-chemical studies in surface chemistry related to offset printing.

1940-1942: Development Assistant. Electronics Planning and Development Laboratory of the Tungsram (Orion) Corporation, Ujpest, Hungary.

PRINCIPAL SCIENTIFIC FINDINGS AND ACCOMPLISHMENTS:

---- Polynuclear aromatic hydrocarbons, phenobarbital, and a variety of other compounds are powerful inhibitors of dimethylnitrosamine demethylase activity, the key enzyme of carcinogenesis by this agent. This is due to repression of the de novo biosynthesis of the enzyme.

---- The ability of polynuclear aromatic hydrocarbons to induce the synthesis of certain microsomal mixed-function oxidases and to repress the synthesis of others depends on critical aspects of molecular size and shape, and the two effects show an exact mirror-image relationship.

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----- The concept that the genes coding for inducible and repressible mixed-function oxidases are located in separate but cascade-coupled operons (or groups of operons).

----- In vivo alkylation of nuclear DNA by nitrosamines leads to the appearance of "puffs" in the double helix ----- prior to excision and repair ----- due to disruption of the base-pairing pattern.

----- The large increase in the number of mitochondria per cell in the liver, during feeding of certain noncarcinogenic azo dyes ----- a phenomenon first noted around 1950 ----- is not due to de novo synthesis of the mitochondria, but to increase of their half-life.

----- The concept of "critical stage" in carcinogenesis, representing the point-of-no-return.

----- The critical stage in azo dye carcinogenesis correlates ----- in the target tissue ----- with specific alterations of: (a) the mitochondrial membrane, involving drastic temporary decrease of swelling-contraction and the temporary appearance of the phenomenon of respiratory release, and (b) the endoplasmic reticulum membrane as indicated by the sharp, temporary decrease of microsomal suspensions to show light-scattering changes attributed to swelling. Covalent binding of azo dyes in the two subcellular particles exclusively to membranes.

----- The sensitivity of the mitochondrial membrane to inducers of swelling decreases progressively in the target tissue of azo dye carcinogenesis and this is coincident with phase-transitions in the membrane.

----- The concept that the decrease of respiration observable in certain azo dye-induced hepatomas is due to electron leak in intermediate segment(s) of the electron transport chain, consequent to the biochemical lesions created by deletion of the molecular system of swelling-contraction.

----- The potent protein denaturing ability of some water-soluble carcinogens and the mechanism of this effect.

----- The carcinogenic activity of dioxane and certain aspects of its mechanism of action.

----- A p'-ethyl group is the strongest potentiator of activity of azo dye carcinogens (and probably aromatic amines).

----- Quantification of the relationship between molecular size of polynuclear aromatic hydrocarbons and their carcinogenic activity.

----- Cardiac hypertrophy of different etiologies all lead to decrease of mitochondrial ATP synthesis, but different patterns of alteration of the energy transducing system are involved.

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----- Alteration of extramitochondrial NADH oxidation and the existence of successive metabolic patterns in progressive thiamine deficiency.

----- In thiamine deficiency, decreased protein synthesis in heart tissue is mediated via decrease of the total ribosomal mass, rather than via the usual regulatory modality, i.e., shift in polysome/monosome ratio.

----- The mitochondrial membrane undergoes progressive changes during aging. The existence of host-transmissible factors regulating the dynamic state of the membrane.

----- The "meso migration," a new type of molecular rearrangement in polynuclear diquinols.

----- Writing of a multi-volume treatise on the "Chemical Induction of Cancer" (Academic Press). Three volumes completed.

GRANTS, AWARDS, FELLOWSHIPS:

1972-76. Faculty Research Award. American Cancer Society.

--- 1971. Principal Investigator. Research Grant-in-Aid, entitled "Inhibition of Azo Dye Carcinogenesis by Noncarcinogenic Analogs: Possible Mediation via Mitochondrial DNA Function," Cancer Association of Greater New Orleans, Inc.

1959- Principal Investigator. Research Grants C-4351 and C-5431, entitled "Finestructural Alterations in Cell Particles," from the National Cancer Institute of the United States Public Health Service.

1960-63. Co-investigator. Research Grant K-62-3, entitled "A Study of Sarcosomes in Normal and Dilated Heart," of the Hospital Division, United States Public Health Service.

--- 1960. Principal Investigator. Research Grant-in-Aid, entitled "Denaturation of Biological Macromolecules by Carcinogenic Agents," from the Greater New Orleans Cancer Association Inc. and the Cancer Society of Greater Baton Rouge.

--- 1950. Award of the Chamber of Dyers and Colorists of the City of Paris for majoring "with felicitations" in dye chemistry.

1948-50. Research Fellowship ("Stagiaire de Recherche"), National Center of Scientific Research (CNRS), Paris, France.

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MEMBERSHIPS IN PROFESSIONAL SOCIETIES:

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Associate Editor: "Cancer Research," 1972-1976.
Editorial advisory board: "Cancer Research," 1968-71.
US National Cancer Plan panelist, Airlie House, December 1971.

LISTINGS IN PROFESSIONAL DIRECTORIES:

American Men of Science, Leaders in American Science.

LANGUAGES: French, German and Hungarian.

FOREIGN TRAVELS:

Resided, and travelled broadly in Central and Western Europe (Hungary, Roumania, Austria, Southern Germany, France, Belgium and England).

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PUBLICATIONS:
(in chronological order)

1. Etienne, A., and Arcos, J. C., "Recherches sur les diquinols mésoamino-diphénylanthracéniques. I. Mésodiphénylanthracènes aminés en para sur les phényles." Bull. Soc. Chim. France, 18, 684-689 (1951).

2. Etienne, A. and Arcos, J. C., "Recherches sur les diquinols mésoamino-diphénylanthracéniques. II. Migration d'aryles des diquinols bis-p-dialcoylaminés sur les phényles." Bull. Soc. Chim. France, 18, 690-693 (1951).

3. Arcos, J. C., "Recherches sur les diquinols mésodiphénylanthracéniques aminés. Étude sur la 'migration méso'." Monograph Soc. Édition Enseignement Supérieur, Paris, 1951 (Printed Doctoral Dissertation).

4. Arcos, J. C. and Miller, J. A., "Synthesis of 2-Amino-5-dimethylaminodiphenylamine and Other Derivatives of 3,4-Dinitrodimethylaniline." J. Am. Chem. Soc., 77, 3128-3129 (1955).

5. Arcos, J. C., Arcos, M., Buu-Hoi, N. P. and Lacassagne, A., "Indices de Valence Libre, Adsorbabilités et Activité Cancerogène des Hydrocarbures Polycycliques." Comptes Rendus Acad. Sci., 241, 836-839 (1955).

6. Arcos, J. C. and Arcos, M., "Activité Cancerogène et Relation Structurale Entre le Graphite et les Hydrocarbures Polycycliques Condensés." Comptes Rendus Acad. Sci., 241, 777-779 (1955).

7. Arcos, J. C. and Arcos, M., "Size and Carcinogenic Activity of the Polycyclic Hydrocarbons." Naturwissenschaften, 42, 608 (1955).

8. Arcos, J. C. and Arcos, M., "Inclusion Compounds and Carcinogenesis: A Stereochemical Model." Naturwissenschaften, 42, 651-652 (1955).

9. Arcos, J. C. and Arcos, M., "Stereochemical Factors in Carcinogenesis." Bull. Soc. Chim. Belges, 65, 5-16 (1956).

10. Arcos, J. C., Arcos M. and Miller, J. A., "Synthesis of Nitro and Amino Derivatives of Benzo(c)cinnoline." J. Org. Chem., 21, 651-654 (1956).

11. Arcos, J. C. and Arcos, M., "Géométrie moleculaire et carcinogénèse chimique." Rev. Fermentations (Belgium), 11, 127-134 (1956).

12. Arcos, M. and Arcos, J. C., "Sur le Rôle Possible du Graphite dans la Biogénèse." Rev. Gen. Sci. et Bull. Assoc. Franc. Avancement des Sciences, 63, 89-100 (1956).

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13. Arcos, J. C. and Arcos, M., "An Evidence for Change in Microsomal Fine-structure During Chemical Carcinogenesis." Naturwissenschaften, 44, 331-332 (1957).

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14. Arcos, J. C., "Studies on the Swelling and Solubilization of Rat Liver Microsomes." Naturwissenschaften, 44, 332 (1957).

15. Arcos, M. and Arcos, J. C., "Sur un mécanisme de l'augmentation de l'activité de composés cancerogènes par certains substituants fluorés et alcoylés." Comptes Rendus Acad. Sci., 245, 1092-1094 (1957).

16. Arcos, J. C. and Arcos, M., "Finestructural Alterations in Cell Particles During Chemical Carcinogenesis. I. Influence of the Feeding of Aminoazo Dyes on the Swelling and Solubilization of Rat Liver Microsomes." Biochim. Biophys. Acta, 28, 9-20 (1958).

17. Lacassagne, A., Arcos, J. C., Buu-Hoi, N. P. and Zajdela, F., "Quelques expériences préliminaires sur le mécanisme de la cancérisation par matières plastiques." Bull. Cancer, 44, 545-551 (1957).

18. Wirtz, G. H. and Arcos, J. C., "Studies on the Dye-Binding Fraction of Soluble Liver Proteins from Rats Fed Aminoazo Dyes." Experientia, 14, 177-178 (1958).

19. Arcos, M. and Arcos, J. C., "A Correlation of Constitution and Carcinogenic Activity. Part I. A Study of the Essential Molecular Parameters." Arzneimittelforschung (Drug Research) 8, 486-489 (1958).

20. Arcos, J. C. and Arcos, M., "A Correlation of Constitution and Carcinogenic Activity. Part II A. Interactions Involving Covalent Bonds of Carcinogens with Proteins in the Cell. An Attempt of Evaluation." Arzneimittelforschung (Drug Research) 8, 602-605 (1958).

21. Arcos, M. and Arcos, J. C., "A Correlation of Constitution and Carcinogenic Activity. Part II B. Interactions Involving Secondary Valence Forces of Carcinogens with Proteins in the Cell. New Developments." Arzneimittelforschung (Drug Research) 8, 643-647 (1958).

22. Arcos, J. C., Griffith, G. W. and Cunningham, R. W., "Studies on the Swelling of Rat Liver Mitochondria in Relation to Tumor Incidence During Feeding of Aminoazo Dyes." Experientia, 15, 316-317 (1959).

23. Arcos, J. C., Griffith, G. W. and Cunningham, R. W., "Finestructural Alterations in Cell Particles During Chemical Carcinogenesis. II. Further Evidence for Their Involvement in the Mechanism of Carcinogenesis. The Swelling of Rat Liver Mitochondria During Feeding of Aminoazo Dyes." J. Biophys.-Biochem. Cytol., 7, 49-60 (1960).

24. Arcos, J. C., Conney, A. H., and Buu-Hoi, N. P., "Induction of Microsomal Enzyme Synthesis by Polycyclic Aromatic Hydrocarbons of Different Molecular Sizes." J. Biol. Chem., 236, 1291-1296 (1961).

25. Arcos, J. C., "Alterations of Microsomal and Mitochondrial Sites of Metabolic Control During Chemical Carcinogenesis." Bull. Tulane Med. Fac., 20, 133-150 (1961).

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26. Gosch, H.H., and Arcos, J.C., "Transmission of Swelling Characteristics by Mitochondria of Regenerating Liver". Nature, 190, 272-273 (1961).

27. Arcos, J.C., Gosch, H.H., and Zickafoose, D., "Finestructural Alterations in Cell Particles During Chemical Carcinogenesis. III. Selective Action of Chemical Carcinogens Other Than 3'-Methyl-4-Dimethylaminoazobenzene. Effect of Stimulated Liver Growth." J. Biophys. Biochem. Cytol., 10, 23-36 (1961).

28. Arcos, J.C., and Griffith, G.W., "Ratio Dependent Synergism in Azo Dye Carcinogenesis". Brit. J. Cancer, 15, 291-298 (1961).

229. Arcos, J.C., and Simon, J., "Effect of 4'-Substituents on the Carcinogenic Activity of 4-Aminoazobenzene Derivatives". Arzneimittelforschung (Drug Research), 12, 270-275 (1962).

30. Gosch, H.H., Arcos, J.C., and Argus, M.F., "Kinetics of Mitochondrial Swelling: Evidence for Specific Receptor Sites for Inducer Compounds." Nature, 195, 1179-1181 (1962).

31. Argus, M.F., Arcos, J.C., and Walder, J.A., "An Evidence for Decrease of Energy Production in Thiamine Deficient Failing Rat Heart." Experientia 28, 519-521 (1962).

32. Argus, M.F., and Arcos, J.C., "Failure of Monochloroacetone to Influence 3,4-Benzpyrene Mouse Skin Tumorigenesis". Experientia, 19; 588-589 (1963).

33. Arcos, J.C., Walder, J.A., and Argus, M.F., "Inhibition and Reversal of Swelling of Rat Heart Sarcosomes by Reduced Diphosphopyridine Nucleotide". Nature, 201, 398-400 (1964).

34. Argus, M.F., Arcos, J.C., Alam, A., and Mathison, J.H., "A Viscometric Study of Hydrogen-Bonding Properties of Carcinogenic Nitrosamines and Related Compounds". J. Medicinal Chem., 7, 460-465 (1964).

35. Arcos, J.C., and Argus, M.F., "A Reconsideration of the Isolation in Presence of EDTA and the Swelling-Contraction Characteristics of Rat Heart Sarcosomes. Metabolic Topography of the Sarcosomal Contractile Protein", Biochemistry, 3, 2028-2040 (1964).

36. Arcos, J.C., Argus, M.F., Sardesai, V.M., and Stacey, R.E., "Effect of Thiamine Deficiency on the Swelling, Electron Transport and Oxidative Phosphorylation of Rat Heart Sarcosomes", Biochemistry, 3, 2041-2045 (1964).

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37. Argus, M.F., Arcos, J.C., Sardesai, V.M., and Overby, J.L., "Oxidative Rates and Phosphorylation in Sarcosomes From Experimentally-Induced Failing Rat Heart", Proc. Soc. Exptl. Biol. Med., 117, 380-383 (1964).

38. Arcos, J.C., Wirtz, G.H., and Arcos, M., "Sur la possibilité de production de tumeurs malignes par des anticorps organo-spécifiques: une méthode de vérification de la théorie d'élimination d'enzyme dans la carcinogénèse chimique expérimentale", Compt. Rend. Acad. Sci., 260, 2371-2373 (1965).

39. Argus, M.F., Arcos, J.C. and Hoch-Ligeti, C., "Studies on the Carcinogenic Activity of Protein Denaturing Agents: Hepatocarcinogenicity of Dioxane". J. Natl. Cancer Inst., 35, 949-958 (1965).

40. Argus, M.F., Arcos, J.C., Mathison, J.H., Alam, A. and Bemis, J.A., "Studies on the Denaturation of Biological Macromolecules by Chemical Carcinogens. I. Aggregation, Viscosity and Optical Rotation Changes Produced in Ovalbumin by Nitrosamines and Other Water-Soluble Carcinogens". Arzneimittelforschung (Drug Research), 16, 740-746 (1966).

41. Argus, M.F., Arcos, J.C., Mathison, J.H. and Alam, A., "Studies on the Denaturation of Biological Macromolecules by Chemical Carcinogens. II. The Reactivity of Sulfhydryl Groups of Ovalbumin. The Sulfhydryl-Disulfide Interchange Mechanism of Aggregation Induced by Nitrosamines and Other Water-Soluble Carcinogens." Arzneimittelforschung (Drug Research), 16, 1083-1088 (1966).

42. Bemis, J.A., Argus, M.F., and Arcos, J.C., "Studies on the Denaturation of Biological Macromolecules by Chemical Carcinogens. III. Optical Rotatory Dispersion and Light-Scattering Changes of Ovalbumin During Denaturation and Aggregation by Water-Soluble Carcinogens". Biochim. Biophys. Acta, 126, 274-285 (1966).

43. Arcos, J.C., Stacey, R.E., Mathison, J.B., and Argus, M.F., "Kinetic Parameters of Mitochondrial Swelling. The Effect of Animal Age. Tissue Distribution of the Mitochondrial "Contractile Protein". Exper. Cell Res., 48, 448-460 (1967).

44. Arcos, J.C., Sohal, R.S., Sun, S.C., Argus, M.F., and Burch, G.E., "Changes in Ultrastructure and Respiratory Control in Mitochondria of Rat Heart Hypertrophied by Exercise". Exper. Mol. Path, 8, 49-65 (1968).

45. Hoch-Ligeti, C., Argus, M.F., and Arcos, J.C., "Combined Carcinogenic Effects of Dimethylnitrosamine and 3-Methylcholanthrene in the Rat". J. Natl. Cancer Inst., 40, 535-549 (1968).

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46. Bemis, J.A., Bryant, G.M., Arcos, J.C., and Argus, M.F., "Swelling and Contraction of Mitochondrial Particles: A Re-examination of the Existence of a Contractile Protein Extractable with 0.6 M-Potassium Chloride". J. Mol. Biol., 33, 299-307 (1968).

47. Argus, M.F., Walder, J.A., Fabian, J.A., and Arcos, J.C., "A Study of Soluble Protein and Sulfhydryl Levels in the Rat Liver during Rapid Normal and Premalignant Growth". Brit. J. Cancer, 22, 330-341 (1968).

48. Venkatesan, N., Arcos, J.C., and Argus, M.F.: "Differential Effect of Polycyclic Hydrocarbons on the Demethylation of the Carcinogen Dimethylnitrosamine by Rat Tissues". Life Sciences, 7, (Part I), 1111-1119 (1968).

49. Arcos, J.C., Mathison, J.B., Tison, M.J., and Mouledoux, A.M., "Effect of Feeding Amino Azo Dyes on Mitochondrial Swelling and Contraction. Kinetic Evidence for Deletion of Membrane Regulatory Sites." Cancer Research, 29, 1288-1297 (1969).

50. Arcos, J.C., Tison, M.J., Gosch, H.H., and Fabian, J.A. "Sequential Alterations in Mitochondrial Inner and Outer Membrane Electron Transport, and in Respiratory Control during Feeding Amino Azo Dyes; Stability of Phosphorylation. Correlation with Swelling-Contraction Changes and Tumorigenesis Threshold". Cancer Research, 29, 1298-1306 (1969).

51. Arcos, J.C., Argus, M.F., and Mathison, J.B., "Hepatic Carcinogenesis Threshold and Biphasic Mitochondrial Swelling Response in the Guinea Pig During Diethylnitrosamine Administration". Experientia, 25, 296-298 (1969).

52. Buu-Hoi, N.P., Saint-Ruf, G., and Arcos, J.C., "Sur quelques hétérocycles dérivés d'orthodiamines pyridiques, pyrimidiques et indazoliques". Bull. Soc. Chim. France 838-842 (1969).

53. Gosch, H.H., Arcos, J.C., and Argus, M.F., "On the Unimpairable Resistance of the Guinea Pig to Dietary Amino Azo Dye Hepatocarcinogenesis". Z. Krebsforsch., 73, 215-217 (1970).

54. Hoch-Ligeti, C., Argus, M.F., and Arcos, J.C., "Induction by Dioxane of Carcinomas in the Nasal Cavity of Rats". Brit. J. Cancer, 24, 164-167 (1970).

55. Wu, B.C., Argus, M.F., and Arcos, J.C., "Differential Decrease of "Shuttle" Enzymes of Extra-mitochondrial $NADH_2$ Oxidation of Heart Muscle during Progressive Thiamine Deficiency". Proc. Soc. Exptl. Biol. Med., 133, 808-812 (1970).

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56. Venkatesan, N., Argus, M.F., and Arcos, J.C., "Mechanism of Methylcholanthrene-Induced Inhibition of Dimethylnitrosamine-Demethylase in Rat Liver". Cancer Res., 30, 2556-2562 (1970).

57. Venkatesan, N., Arcos, J.C., and Argus, M.F., "Amino Acid Induction and Carbohydrate Repression of Dimethylnitrosamine-Demethylase in Rat Liver". Cancer Res., 30, 2563-2567 (1970).

58. Arcos, J.C., "Ultrastructural Alteration of the Electron Transport Chain Involving Electron Leak: Possible Basis of "Respiratory Impairment" in Certain Tumors." J. Theoret. Biol. 30, 533-543 (1971).

59. Argus, M.F., White, L.E., Bryant, G.M., Arcos, J.C., and Hoch-Ligeti, C., "Molecular Specificity of the Tumorigenic Action of Ethionine; the Inactivity of S-Ethylcysteine. Action on Respiratory Parameters". Z. Krebsforsch., 75, 201-208 (1971).

60. Wu, B.C., Arcos, J.C., and Argus, M.F., "Polysome Profile and Change in Total Ribosomal Mass in Rat Heart During Progressive Thiamine Deficiency". Life Sciences, 10 (Part II), 541-551 (1971).

61. Venkatesan, N., Arcos, J.C., and Argus, M.F., "Induction and Repression of Microsomal Drug-Metabolizing Enzymes by Polycyclic Hydrocarbons and Phenobarbital: Theoretical Models". J. Theoret. Biol., 33, 517-537 (1971).

62. Argus, M.F., Valle, R.T., Venkatesan, N., Buu-Hoi, N.P., and Arcos, J.C., "Molecular Size-Dependent Effects of Polynuclear Hydrocarbons on Mixed-Function Oxidases: Possible Action on Cascade-Coupled Operons". Proceedings First Europ. Biophys. Congr. (Vienna) 1 (EI/38), 187-192 (1971).

63. Wu, B.C., Valle, R.T., White, L.E., Sohal, R.S., Arcos, J.C., Argus, M.F., and Burch, G.E., "Alterations in the Energy Transducing System and Mitochondrial Ultrastructure of Rat Heart During Progressive Thiamine Deficiency". Virchows Arch. Abt. B Zellpath. 9, 97-114 (1971).

64. Arcos, J.C., Venkatesan, N., and Argus, M.F., "Modification of the Flow Dichroism Spectrum of Rat Liver Nuclear DNA by In Vivo Alkylation with Heptocarcinogenic Dialkylnitrosamines". Gann (Japanese J. Cancer Res.) 62, 523-533 (1971).

65. Buu-Hoi, N.P., Saint-Ruf, G., and Arcos, J.C., "Synthèse, Structure et Propriétés de Dérivés Nouveaux de Triaza-, Tetraaza- et Pentaaza--benz [a] anthracènes." Bull. Soc. Chim. France 2028-2032 (1972).

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66. Argus, M. F., Sohal, R. S., Bryant, G. M., Hoch-Ligeti, C., and Arcos, J. C., "Dose-response and Ultrastructural Alterations in Dioxane Carcinogenesis. Influence of Methylcholanthrene on Acute Toxicity." Europ. J. Cancer, 9, 237-246 (1973).

67. Wu, B. C., Arcos, J. C., and Argus, M. F.: "Control of Catabolism of Mitochondria in Oncogenesis. I. Increase of Hepatic Mitochondrial Population During Feeding Inactive or Marginally Active Amino Azo Dyes: Absence of de Novo Biosynthesis". Submitted for publication.

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Monographs and Contributions to Review Series & Symposia.

1. Arcos, J. C., and Arcos, M.: "Molecular Geometry and Mechanisms of Action of Chemical Carcinogens." In "Progress in Drug Research," Jucker, E., Editor, Birkhäuser, Basel, Vol. 4, 1962, pp. 407-581.

2. Arcos, J. C.: "Carcinogenic Substances." In "Encyclopedia of Biochemistry," Williams, R. J., and Lansford, E. M., Eds., Reinhold, New York, 1967, pp. 192-196.

3. Arcos, J. C., Argus, M. F. and Wolf, G.: "Chemical Induction of Cancer — Structural Bases and Biological Mechanisms" Vol. I. (This volume contains Part I. Molecular architecture and the physical bases of molecular forces; and Part II. The nature of tumors. Concepts and techniques of testing chemical agents for carcinogenic activity.) Academic Press, New York, 1968, 491 pages.

4. Arcos, J. C., and Argus, M. F.: "Molecular Geometry and Carcinogenic Activity of Aromatic Compounds. New Perspectives." In "Advances in Cancer Research," Academic Press, New York, Vol. 11, 1968, pp. 305-471.

5. Arcos, J. C.: "French Research on Chemical Carcinogenesis in the Last Quarter Century with Special Reference to the Contributions of A. Lacassagne and N. P. Buu-Hoi." Proceedings of "World Symposium on Model Studies in Chemical Carcinogenesis," Baltimore, Oct. 31-Nov. 3, 1972. Marcel Dekker publ., in press.

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CURRICULUM VITAE OF MARY FRANCES ARGUS

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Education;

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Secondary - St. Joseph High School, Ironton, Ohio (

R

Latin Scientific Course; Valedictorian; Recipient of four year college tuition scholarship.

Undergraduate - B. S. (magna cum laude) (Major-Chemistry, Minors-Mathematics, English; Certificate to teach Science, Mathematics and English in Secondary Schools in the State of Ohio) -

R

College of Mount Saint Joseph-on-the-Ohio, Cincinnati, Ohio.

Graduate - M. S. (Major- Organic Chemistry, Minor-Physical Chemistry, Thesis - "Sulfur Derivatives of Fluorene") - June 1947 - University of Cincinnati, Cincinnati, Ohio.

Ph. D. (Major-Oncology, Minor-Pharmacology, Thesis - "New Compounds for Cancer Research. The Synthesis and Metabolic Study of Isotopic Derivatives of Fluorene.") - February 1952 - University of Florida, Gainesville, Florida.

Specialized - Oak Ridge Institute of Nuclear Studies: Advanced Course for Biochemists - November; 1952; Course in Advanced Instrumentation - July, 1954. American Chemical Society Short Course in "Molecular Orbital Theory", Houston, 1969. The Jackson Laboratory "Short Course in Mammalian Genetics", Bar Harbor, Maine, 1969.

Professional Experience:

September 1945 - June 1947 - Assistant Instructor of General and Organic Chemistry, University of Cincinnati , Cincinnati, Ohio.

September 1947 - June 1949 - Instructor of General, Organic and Biochemistry, Marygrove College, Detroit, Michigan.

February 1952 - June 1956 - Assistant Research Professor in charge of Biochemistry Section, Cancer Research Laboratory, University of Florida, Gainesville, Florida.

July 1956 - October 1960 - Associate Research Professor in charge of Biochemistry Section, Cancer Research Laboratory (affiliated with Dept. of Pharmaceutical Chemistry, College of Pharmacy from July, 1959), University of Florida, Gainesville, Florida.

November, 1960 - May, 1968 - Associate Professor of Medicine (Biochemistry), Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana, and Seamen's Memorial Research Laboratory, U.S. Public Health Service Hospital, New Orleans, La.

May, 1968 - - Professor of Medicine (Biochemistry), Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana, and Seamen's Memorial Research Laboratory, U.S. Public Health Service Hospital, New Orleans, La.

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Professional Organizations:

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Listed in: American Men of Science, Who's Who of American Women, Leaders in American Science.

Research Grants:

1. Atomic Energy Commission Contract AT-(40-1)-2097
   "Studies of Radiation and Chemical Carcinogenesis"

2. U.S. Public Health Service Research Grant C-1356
   "Localization of Radioactive Compounds in Tumors"

3. U.S. Public Health Service Research Grant CY-4939
   "Mechanism of Nitrosamine Carcinogenesis"

4. Greater New Orleans Cancer Association
   "Denaturation of Biological Macromolecules by Carcinogenic Agents"

5. U.S. Public Health Service Research Grant C-5793
   "Mechanism of Nitrosamine Carcinogenesis"

6. Division of Hospitals, U.S. Public Health Service, Grant K62-3
   "Study of Sarcosomes in Normal & Dilated Heart"

7. Greater New Orleans Cancer Association
   "Mechanism of Gene-Level Inhibition of Carcinogenesis"

8. U.S. Public Health Service Research Grant CA-13206
   "Pharmacology of Repressible Mixed-Function Oxidases"

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3. Ray, F.E. and Argus, M.F. - Studies on the Metabolism, Distribution and Excretion of 2-p-Toluenesulfonamindofluorene-S^{35} in the Rat. Cancer Research, 11: 783-787 (1951).

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52. Venkatesan, N., Arcos, J. C. and Argus, M. F. Differential Effect of Polycyclic Hydrocarbons on the Demethylation of the Carcinogen Dimethylnitrosamine by Rat Tissues. Life Sciences, 7 (Part I): 1111-1119 (1968).

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54. Gosch, H. H., Arcos, J. C. and Argus, M. F. On the Unimpairable Resistance of the Guinea Pig to Dietary Amino Azo Dye Hepatocarcinogenesis. Z. Krebsforsch., 73: 215-217 (1970).

55. Wu, B. C., Argus, M. F. and Arcos, J. C. Differential Decrease of "Shuttle" Enzymes of Extra-Mitochondrial $NADH_2$ Oxidation of Heart Muscle during Progressive Thiamine Deficiency. Proc. Soc. Exptl. Biol. Med., 133: 808-812 (1970).

56. Hoch-Ligeti, C., Argus, M. F. and Arcos, J. C. Induction by Dioxane of Carcinomas in the Nasal Cavity of Rats. Brit. J. Cancer, 24: 164-167 (1970).

57. Venkatesan, N., Argus, M. F., and Arcos, J. C. Mechanism of Methylcholanthrene-Induced Inhibition of Dimethylnitrosamine Demethylase in the Rat Liver. Cancer Research, 30: 2556-2562 (1970).

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Mary F. Argus Curriculum Vitae continued

59. Argus, M.F., White, L.E., Bryant, G.M., Arcos, J.C., and Hoch-Ligeti, C. Molecular Specificity of the Tumorigenic Action of Ethionine; the Inactivity of S-Ethylcysteine. Action on Respiratory Parameters. Z. Krebsforsch., 75: 201-208 (1971).

60. Wu, B.C., Arcos, J.C., and Argus, M.F. Polysome Profile and Change in Total Ribosomal Mass in Rat Heart During Progressive Thiamine Deficiency. Life Sciences, 10 (Part II): 541-551 (1971).

61. Argus, M.F. Susceptibility of the Guinea Pig to Chemical Carcinogenesis. Cancer Res., 31: 917-918 (1971).

62. Argus, M.F., Valle, R.T., Venkatesan, N., Buu-Hoi, N.P., and Arcos, J.C. Molecular Size-Dependent Effects of Polynuclear Hydrocarbons on Mixed-Function Oxidases: Possible Action on Cascade-Coupled Operons. Proceedings First Europ. Biophys. Congr. (Vienna), I (EI/38): 187-192 (1971).

63. Wu, B.C., Valle, R.T., White, L.E., Sohal, R.S., Arcos, J.C., Argus, M.F., and Burch, G.E. Alterations in the Energy Transducing System and Mitochondrial Ultrastructure of Rat Heart During Progressive Thiamine Deficiency. Virchows Arch. Abt. B Zellpath., 9: 97-114 (1971).

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65. Venkatesan, N., Arcos, J.C., and Argus, M.F. Induction and Repression of Microsomal Drug-Metabolizing Enzymes by Polycyclic Hydrocarbons and Phenobarbital: Theoretical Models. J. Theoret. Biol., 33: 517-537 (1971).

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BOOKS AND CONTRIBUTIONS TO MULTI-AUTHOR VOLUMES

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3. Hoch-Ligeti, C., and Argus, M.F.: "Effect of Carcinogens on the Lung of Guinea Pigs". In "Morphology of Experimental Respiratory Carcinogenesis", Nettesheim, P., Hanna, M.G., and Deatherage, J.W., eds., AEC Symp. No. 21, Div. Techn. Info., US Atomic Energy Commission. Oak Ridge, Tenn., 1970, pp. 267-279.

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Mary F. Argus Curriculum Vitae continued Abstract Publications Continued

24. Venkatesan, N., Arcos, J.C., and Argus, M.F.: "Regulatory Mechanisms in the Demethylation of Dimethylnitrosamine (DMN)". Abstract 15, page 11-12, Tenth International Cancer Congress, Houston, 1970.

25. Arcos, J.C., Bryant, G.M., and Argus, M.F.: "Stereoselective Uncoupling of Oxidative Phosphorylation by Aliphatic Dicarbonyls: Probes in Azo Dye Carcinogenesis". Abstract 74, page 48-49, Tenth International Cancer Congress, Houston, 1970.

26. Hoch-Ligeti, C. and Argus, M.F.: "Effect of Carcinogens on the Lung of Guinea Pigs." Conference on Morphology of Experimental Respiratory Carcinogenesis, Gatlinburg, Tenn., 1970.

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CURRICULUM VITAE

NAME: Joseph Simon

ADDRESS: REDACTED

BORN: REDACTED

FAMILY: REDACTED

EDUCATION:

Cornell University	1936-1940	B.S.	Dairy Manufacturing
Texas A. and M. College	1941-1942	M.S.	Dairy Manufacturing
Kansas State College	1943-1946	D.V.M.	Veterinary Medicine
University of Wisconsin	1948-1951	Ph.D.	Veterinary Medicine Pathology and Bacteriology

1946-1948 Veterinary Practice and Regulatory Work
1948-1958 Instructor and Assistant Professor, Department of Veterinary Science, University of Wisconsin, Madison, Wisconsin
September 1958 to May 1960 Research Associate Professor, Cancer Research Laboratory, University of Florida, Gainesville, Florida
May 1960 to Present Professor Pathology, Hygiene and Veterinary Research College of Veterinary Medicine, University of Illinois, Urbana, Illinois

RESEARCH: Projects pertaining to bovine mastitis, reproductive diseases of dairy cattle and mycotic agents of importance to cattle, including microbiological, pathological, therapeutic and field aspects of these problems; experimental pathology pertaining to carcinogenesis of various agents. Supervision of graduate students, technicians, farm laborers, animal caretakers and part-time workers. Approximately 90 scientific papers published.

TEACHING: Courses in Veterinary Pathology for undergraduate and graduate students, course in oncology for graduate students, charge of clinical-pathologic conference for 3rd and 4th year students.

CONSULTATION: (a) Members of the Animal Disease Diagnostic Laboratory of the State of Wisconsin, local veterinary practitioners, dairy field men and farmers. Much of the work consisted of gross and histopathology as well as bacteriology.
(b) Projects in the Departments of Agronomy, Genetics, Bacteriology and Dairy Industry at the University of Wisconsin.
(c) Departments of Veterinary Science and Bacteriology at the University of Florida.
(d) Departments of Dairy Science and Animal Nutrition, University of Illinois.

VETERINARY EXPERIENCE: Approximately two years in practice prior to entrance into the graduate school of the University of Wisconsin in 1948.

VETERINARY LICENSING: Wisconsin, Montana, Kansas and Missouri

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PROFESSIONAL SOCIETY MEMBERSHIPS:

HONORARY SOCIETY MEMBERSHIPS:

MISCELLANEOUS AFFILIATIONS

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